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EXAMINER	
GROSS, CHRISTOPHER M	

ART UNIT	PAPER NUMBER
1639	

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11/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,799	MEHTA ET AL.	
	Examiner	Art Unit	
	Christopher M. Gross	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44 and 51-55* is/are pending in the application.

4a) Of the above claim(s) *6,8,10,13,16,18,19,28 and 32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, 9, 11-12, 14-15, 17, 20-27, 29-31, 36-44, 51-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☑ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/3/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Responsive to communications entered 8/27/2007. Claims 1-44,51-55 are pending. Claims 6, 8, 10, 13,16, 18-19, 28, 32-35 are withdrawn. Claims 1-5, 7, 9, 11-12, 14-15, 17, 20-27, 29-31, 36-44, 51-55 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) is again acknowledged. This application claims benefit of provisional application 60/453,629 filed 03/10/2003.

Information Disclosure Statement

Citations 5,8, 11-12, 19-22, 27,29-32,34-37,39,43,44,47,48,50,53,56,60,63, 67,70,76,78, 79,81,83,86,88, 93-95,97,101,104-105, 109,120, 128, 131, 133, 136 and 137 of the information disclosure statement filed 9/3/2004 have been considered to the extent of the abstract.

The information disclosure statement entered 9/3/2004 remains objected to because relevant pages, and date and place of publication are missing from some of the non-patent documents [See MPEP 609.01, (B)(1)(e)(v)]. It is not possible for the Examiner to consider citations 17-18, 64, 132 without a proper date. See also 37 CFR 1.98

Withdrawn Objection(s) and/or Rejection(s)

The rejection of claims 1-5,7,9,11-12, 14-15, 17, 20-27, 29-31, 36-44 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention concerning: "deranged cell signaling pathways" in claim 1; the past-tense use of the term "selected" in claim 1; lack of antecedent basis for "the subject" in line 3 of claim 3; and "prior success" in claim 24 is hereby withdrawn in view of applicant's amendments to the claims.

The provisional rejection of claims 1 and 25 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/189808 in view of **Bishop et al** (US Patent 6,316,462) and in further view of **Jain et al** (2000 IEEE Transactions on Pattern Analysis and Machine Intelligence 22:4-37 – IDS entry 9/3/2004) is hereby withdrawn in view of applicant's cancellation of claim 1 in application 11/189808.

Maintained Claim Rejection(s) - 35 USC § 102

Claims 1,2,7,14-15,20-23,36-39,41-42 are rejected under 35 U.S.C. 102(b) as being anticipated by **Bishop et al** (US Patent 6316462).

Response to Arguments

Applicant argues not all elements are taught.

Applicant's arguments have been fully considered but they are not deemed persuasive for the following reasons.

Specifically, applicant argues see p 13 (8/27/2007) Bishop et al do not teach the "diseased cell," set forth in claim 1, which is defined in the present specification "a cell that is identifiable...as being involved in a pathological condition in a tissue" in that the cells of Bishop et al are ras transformed Rat1 and Rat2 fibroblasts. In this regard, solely to rebut applicant's argument, evidence provided by Nasser et al (2006 Current Topics in Medicinal Chemistry 6:1109-1116) indicates otherwise. In the abstract, Nasser et al state, "Rho GTPases of the Ras superfamily are involved in multiple cell functions and have been implicated in the pathology of various human diseases including cancer." Emphasis added.

Applicant asserts, see last paragraph p 13 (8/27/2007) that claim 1 has been amended to include the method step of "measuring activity states for a plurality of different signaling proteins from a **reference cell.**" It is noted, however Bishop et al teach, particularly in figure 5 bars 5-8, and the paragraph bridging columns 3 and 4, a comparison of caspase activation (apoptotic potential) in ras transformed Rat2 cells vs. parental (control) Rat2 cells. It is the examiner's position that the control Rat2 cells of Bishop et al constitute a "reference" cell and further the ras transformed Rat2 cells are "diseased," especially in view of the passage of Nasser et al mentioned above.

Applicant further asserts, see first paragraph p 14 (8/27/2007) that Bishop et al do not teach "**determining whether the activity states measured for the plurality of signaling proteins extracted from the diseased cell are different** than the activity states of the reference cell," because, applicant argues, caspase activity, is not indicative of the activity state of a plurality of signaling proteins.

In this regard, solely to rebut applicant's argument, evidence provided by Thornberry et al (1998 Science 281:1312-1316) indicates caspase activity is, in fact, involved in a multitude of biological pathways. Thornberry et al state on p 1314, right column, second full paragraph that caspases cut off contacts with surrounding cells, reorganize the cytoskeleten, shut down DNA replication and repair, interrupt splicing, destroy DNA, disrupt nuclear structure, induce the cell to display signals that mark it for phagocytosis, etc. In particular, Thornberry et al indicate, for example, in the paragraph bridging the left and right columns on p 1314 caspases cleave FAK (focal adhesion kinase) and PAK2 (p21 activated kinase). Thus, it is the examiners position that in measuring extracted caspase activity, Bishop et al discern the activity state of many downstream proteins such as FAK and PAK2, albeit indirectly.

Lastly, applicant contends, see p 14 (8/27/2007), that Bishop et al do not teach "selecting a combination of at least two therapeutic agents which **reduce the difference** in activity state between the diseased and reference cell." In this regard, as mentioned in the previous office action, applicant's attention is respectfully invited to figure 6 of Bishop et al which indicates both PD098059 and SCH 66336 prevent phosphorlyation of ERK 1 and 2, present in the constitutively active ras pathway shown in figure 1, according to Bishop et al, therein reducing the difference between Erk activity in the ras transformed Rat2 "diseased" versus the parental control "reference" Rat2 cells.

Maintained Claim Rejection(s) - 35 USC § 103

Claims 1,2,7,14-15,20-23,36-39,41-42 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Bishop et al** (US Patent 6,316,462) in view of **Lubman et al** (US Patent Application 2005/0230315).

Response to Arguments

Applicant argues Lubman et al does not constitute prior art.

Applicant's arguments have been fully considered but they are not deemed persuasive for the following reasons.

Specifically, Applicant argues, see p 17 (8/27/2007) that support for antibodies to phosphoproteins can not be found in provisional application 60/439625 to Lubman et al, required to antedate the present application under 35 USC 102(e), however applicant's attention is respectfully invited to p 7, lines 29-30 of provision application 60/439625 where Lubman et al first envision embodiments concerning selective antibody binding: "the protein microarray is analyzed to detect antibody binding (e.g., to identity antibodies that differentially bind from the experimental sample to a different degree than those from a control sample)."

Second, differences between microarrays derived from experimental vs. control samples include mass spectometric based detection of phosphorlyation according to Lubman et al on p 57, lines 13-15 of provision application 60/439625: "...it is contemplated that one cam [sic] determine the relative abundances of the phosphorylated and non-phosphorylated forms of a given protein"

Finally, on p 34 lines 14-15 of provision application 60/439625, Lubman et al state the microarray, in addition to analysis by mass spectrometry, may be probed with

immunoglobulins: "Thus all information obtained about a given 2-D image, including detailed mass spectra, data analyses, and complementary experiments (e.g., immuno-affinity and peptide sequencing) can be accessed from the original image." Emphasis added.

In conclusion, it is the examiner's position that the complementary immuno-affinity experiments of Lubman et al would necessarily include antibodies with affinity for a given protein. In other words, an antibody raised against the non-phosphorylated portion of a protein would specifically bind (i.e. not other proteins) a particular phosphorylated signaling protein, such as set forth in claim 12, in addition to the same signaling protein in un-phosphorylated form.

Therefore, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., utilizing antibodies directed against phosphoserine, phosphothreonine or phosphotyrosine) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claims 1,2,7,14-15,20-23,36-39,41-42 and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Bishop et al** (US Patent 6,316,462) in view of **Moller et al** (US Patent 6,626,044).

Response to Arguments

Applicant argues that there is no motivation to combine Bishop et al with Moller et al.

Applicant's arguments have been fully considered but they are not deemed persuasive for the following reasons.

Specifically, applicant argues, see p 18 (8/27/2007) that the combination of the kinase inhibitors of Bishop et al with the phosphatase inhibitors of Moller et al would render the method of treatment according to Bishop et al inoperable because the phosphatase inhibitors would work against the kinase inhibitors. However, as mentioned in the last office action, the Examiner is *not* suggesting combining the entirety of Bishop et al with Moller et al, rather only the assay portion. In other words, the phosphatase inhibitors of Moller et al would be *substituted* for the kinase inhibitors (i.e. see office action mailed 12/5/2006 p15 last paragraph "It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to use the phosphatase inhibitors of Moller et al in lieu of the Ras pathway Inhibitor(s) in the ERK assay of Bishop et al." Emphasis added). And in this vein the court has stated, "[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." In re Preda, 401 F.2d 825, 826, 159 USPQ 342; 344 (CCPA 1968).

Claims 1,2,7,14-15,20-23,36-39,41-42 and 3-5,9 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Bishop et al** (US Patent 6,316,462) in view of **Bonner et al** (US Patent 6,251,516).

Claims 1,2,7,14-15,20-23,36-39,41-42 and 26,27,29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Bishop et al** (US Patent 6,316,462) in view of **Bilodeau et al** (US Patent Application 2002/0137755) as evidenced by Tortora et al (Clinical Cancer Research 9:1566-1572).

Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Bishop et al** (US Patent 6,316,462) **in view of Bilodeau et al** (US Patent Application 2002/0137755) as applied to claims 1,2,7,14-15,20-23,36-39,41-42 and 26,27,29-31 above, and further in view of **Bonner et al** (US Patent 6,251,516) as evidenced by Tortora et al (Clinical Cancer Research 9:1566-1572) and Moon et al (US Patent Application 2005/0282849)

Claims 1,2,7,14-15,20-23,36-39,41-42and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Bishop et al** (US Patent 6,316,462) in view of **Jain et al** (2000 IEEE Transactions on Pattern Analysis and Machine Intelligence 22:4-37 – IDS entry 9/3/2004).

Response to Arguments

Applicant does not offer further arguments regarding the above obviousness rejections beyond what was set forth with regard to the 35 U.S.C. § 102 rejection. To the extent that Applicant is merely repeating their previous argument, the Examiner

contends that those issues were adequately addressed in the above sections, which are incorporated in their entireties herein by reference.

New Claim Rejection(s) – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 51-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Paweletz et al** (2001 Oncogene 20:1981-1989 - IDS entry 9/3/2004) in view of **Bishop et al** (US Patent 6,316,462).

This rejection is necessitated by Applicant's amendment to the claims.

The claimed subject matter per new claim 51 is drawn to a method for selecting a combination of therapeutic agents for treatment of a disease caused by a abnormal cell

signaling pathway or a cell signaling pathway network that leads to an aberrant cellular response, comprising:

[i] measuring activity states for a plurality of different signaling proteins extracted from a diseased cell obtained from a subject, wherein the signaling proteins are members of one or more signaling pathways or networks;

[ii] determining whether the activity states measured for the plurality of signaling proteins extracted from the diseased cell are different than activity states measured for corresponding signaling proteins from a reference cell to detect differences between the activity states of individual signaling proteins from the diseased cell and the activity states of the corresponding individual signaling proteins from the reference cell, wherein measuring the activity states of the plurality of signaling proteins comprises using reverse phase protein microarray analysis of phosphorylated signaling proteins using antibodies that specifically bind to a particular phosphorylated signaling protein; and

[iii] selecting a combination of at least two different therapeutic agents that target two or more different members of a protein signaling pathway or network comprising an individual signaling protein for which a difference in activity state was detected between the diseased cell and the reference cell, wherein the agents reduce the difference in the activity state that was detected.

Claims 52-55 represent variations thereof.

Paweletz et al teach, throughout the document and especially the title, abstract and figure 5 a reverse phase protein microarray based assay for phosphorylation states

of proteins such as ERK and Akt. Paweletz et al disclose on p 1987 under 'Materials' that samples were from patients at the Shanxi Cancer Hospital in China.

Said measurement of protein phosphorylation states is taken as providing the measuring activity states of claim 51 part [i] and 55.

Paweletz et al teach in figure 1 and p 1982 last paragraph, said microarray comprises, normal, pre-malignant, invasive and stromal tissue, prepared by laser capture microdissection. Said normal tissue provides "reference cells" to which the extent of phosphorlation of ERK and Akt may be compared in "diseased cells", and Paweletz et al conclude in the abstract cancer progression is associated with an increase of Akt phosphorlation and supression of caspase mediatied apoptosis pathways. Said phosphorylation is measured using and Phospho-Akt specific antibodies per figure 5.

Said conclusion of Paweletz et al is taken as the determining whether the activity states measured for the plurality of signaling proteins extracted from the diseased cell are different than activity states measured for corresponding signaling proteins from a reference cell of claim 51 part [ii].

Said laser capture microdissection reads on claim 54, the microdissection of claim 53 and the isolation of claim 52.

Paweletz et al do not teach selecting a combination of at least two different therapeutic agents that target two or more different members of a protein signaling pathway or network comprising an individual signaling protein for which a difference in

activity state was detected between the diseased cell and the reference cell, wherein the agents reduce the difference in the activity state that was detected.

Bishop et al teach, throughout the document, and especially the abstract and figure 1 a method for treating cancer comprising a farnesyl transferase inhibitor (e.g. SCH 66336) and additional Ras signaling pathway inhibitors (e.g. PD 98059 or U0126) as drug candidates. Bishop teach SCH 66335 and U0126 each individually reduce Erk phosphorlyation in ras transformed Rat2 cells in figure 5 and selectively induce apoptosis in ras transformed cells when SCH 66335 and U0126 are combined in figure 6.

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to use the reverse phase protein microarray based analysis of phosphorylation states of Paweletz et al to select farnesyl transferase inhibitors additional Ras signaling pathway inhibitors per Bishop et al.

One of ordinary skill in the art would have been motivated to use the reverse phase protein microarray based analysis of phosphorylation states of Paweletz et al to select farnesyl transferase inhibitors additional Ras signaling pathway inhibitors per Bishop et al because it provides insights about molecular events taking place during disease progression in actual patients and would have provided the means to analyze proteomic changes after treatment in as noted by Paweletz et al in the paragraph bridging the left and right columns on p 1987.

One of ordinary skill in the art would have had a reasonable expectation of success in combining the reverse phase protein microarray based analysis of

phosphorylation states of Paweletz et al to select farnesyl transferase inhibitors additional Ras signaling pathway inhibitors per Bishop et a because both analzye Erk and caspase activity, thus the drug candidates of of Bishop et al are directed to the same proteins and/or pathways that concern Paweletz et al.

New Claim Rejection(s) – 35 USC § 112

The following is a quotation of the **second** paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-5,11-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is necessitated by Applicant's amendment to the claims.

Claim 11 has been amended to insert the limitation "wherein measuring the activity states of the plurality of signaling proteins..." The antecedent basis for this limitation is ambiguous as claim 1 has two steps related to measuring the activity states of the plurality of signaling proteins.

Claim 3 is reproduced below:

> The method of claim 1, wherein the diseased cell is obtained from tissue of ***the subject***, the method further comprising isolating the diseased cell from the tissue of the subject. [emphasis added]

With all due respect, there is insufficient antecedent basis for the first instance of "the subject" in the claim, as indicated above.

Therefore, claims 3,11 and all dependent claims are rejected under 35 USC 112, second paragraph.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Gross whose telephone number is (571)272-4446. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz can be reached on 571 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.usptó.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christopher M Gross
Examiner
Art Unit 1639

cg

/Jon D. Epperson/
Primary Examiner, AU 1639